(a) a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding region thereof, that binds to an aminophospholipid; or

(b) a therapeutically effective amount of an anti-cancer agent.

42. (New) A kit comprising at least a first antibody that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells in an amount effective to induce tumor necrosis, tumor regression or tumor destruction upon administration to an animal with a vascularized tumor; said kit further comprising:

(a) a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding region thereof, that binds to an aminophospholipid; or

(b) a therapeutically effective amount of an anti-cancer agent.

RESPONSE

I. Status of the Claims

Prior to the present Action, claims 1-30 and 34-38 were pending (see **Section III** for discussion of species). Presently, no claims have been amended or canceled. Claims 39-42 have been added, which are fully supported by the application as filed and are unified with the examined claims.

Claims 1-30 and 34-42 are therefore in the case. In accordance with 37 C.F.R. § 1.121, a copy of the pending claims is attached hereto as **Exhibit A**, wherein the claims are labeled as "(New)", where appropriate. As no claims have been amended, a separate exhibit is not necessary.

II. Support for the Claims

Support for the newly added claims is to be found throughout the original specification as filed. Any small entity fees necessary for the introduction of the new claims should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4001.002282.

In claims 39-42, the term "antibody, or an antigen-binding fragment thereof" has been replaced by "antibody". This is supported throughout the application as filed, as exemplified by the alternative recitation in many of the claims, original claim 4 and in extensive sections of the specification. In each of claims 39-42, the "effective amount" of the antibody recited in the claimed kits is even more clearly related to a specific biological function. Support for each of claims 39-42 exists in claim 1 and throughout the specification, as exemplified below.

In claim 39, the antibody is present in an amount effective to kill at least a portion of the tumor vascular endothelial cells upon administration to an animal with a vascularized tumor. This is supported throughout the specification, *e.g.*, at least at page 5, line 20 through page 6, line 2, as supplemented by pages 8 and 9.

The antibody in claim 40 is defined as being present in an amount effective to induce apoptosis or cell death in at least a portion of the tumor vascular endothelial cells upon administration to an animal with a vascularized tumor. This is supported throughout the specification, *e.g.*, at least in the paragraph bridging pages 12 and 13 and at page 14, lines 15-27, particularly lines 23-25.

In each of claims 40-42, the "effective amounts" of the components recited in elements (a) and (b) are also even more precisely related to a specific biological function. In particular, to "a diagnostically effective amount" of the recited detectably-labeled antibody and to "a therapeutically effective amount" of an anti-cancer agent. These terms are also supported

throughout the specification, *e.g.*, at least at pages 28-31, 35-36 and 113-118, particularly at page 28, line 25, page 29, line 16, page 30, line 4, page 31, lines 13 and 27, pages 35-36 and page 117, line 23 (diagnostically effective); and at pages 32-36 and 118-146; see in particular, page 12, lines 25-26, page 31, line 30 and page 32, lines 2-3 (therapeutically effective).

In claim 41, the antibody is present in an amount effective to occlude or destroy at least a portion of the tumor blood vessels upon administration to an animal with a vascularized tumor. This is supported throughout the specification, *e.g.*, at least at page 8, line 7 through page 9, line 3, particularly at page 8, line 29.

Finally, in claim 42, the antibody is present in an amount effective to induce tumor necrosis, tumor regression and/or tumor destruction upon administration to an animal with a vascularized tumor. This is supported throughout the specification, *e.g.*, at least at pages 5, 8-12, 15 and 16, particularly at page 5, lines 5-10, page 8, line 23 through page 9, line 15, page 10, lines 7-12, page 11, lines 17-20, page 12, lines 1-20, page 15, lines 5-11 and page 16, lines 22-28.

It will therefore be understood that no new matter is included within the new claims.

III. Restriction and Species Issues

The original claims are now characterized as being drawn to two distinct inventions, with Applicants electing the Group I invention, of claims 1-30 and 34-38.

Claims 31-33 had earlier been canceled as drawn to a non-elected invention, despite the presence of linking claims and without prejudice to the reinstatement of the canceled claims into this application upon allowance of one or more linking claims. In response to the Action's comments at page 3, third paragraph, only claims 31-33 are drawn to the non-elected *invention* and these claims have already been canceled.

Although the issue is moot as the present response establishes that the generic claims are in condition for allowance, the Office identifies the claims reading on the initially elected species differently at various points, as follows: summary page, claims 1, 3-12, 14, 15 and 19-29; at page 2, claims 1, 3-11, 14, 15 and 19-29; and at page 3, claims 1-12, 14, 15 and 19-29.

As acknowledged in the Action at page 3, second paragraph, claims 1-30 and 34-38 were pending when the Action was written. The Action is therefore in error in the statement earlier in this paragraph that "claims 2, 13, 16-18 and 30-38 are withdrawn from further consideration" (emphasis added). These claims are not withdrawn from *further* consideration; in fact, as the present response confirms allowability of the generic claims, the claims drawn to the originally non-elected species must now be rejoined in the case.

IV. Specification

The Action at pages 12 and 13 includes certain comments concerning the practice of "incorporation by reference" in U.S. patent law. It is Applicants' position that the present disclosure teaches those of ordinary skill in the art how to make and use the claimed invention without undue experimentation. In the absence of a rejection of all claims under 35 U.S.C. § 112, first paragraph, it appears that the Office agrees with this position.

V. Information Disclosure Statement

At page 13, the Action comments on certain Information Disclosure Statements (IDSs) already of record. Although the Action is not completely clear, it appears that certain of the references already supplied could not be readily located in the Office, *i.e.*, those references that have been "crossed out" on the copy of the 1449 returned to the Applicants.

Applicants respectfully point out that all references were evidently received in the Office, as indicated by the date-stamped, return postcards received by Applicants' representatives.

Nonetheless, additional copies of those references that have been crossed out on the returned 1449 are enclosed herewith and Applicants request that they be considered and entered into the record. In the unlikely event that the Office chooses to use any of these originally disclosed references in a rejection under 35 U.S.C. § 102 or § 103, Applicants also respectfully point out that this would have to be made as part of a non-final Official Action.

VI. Summary

The presently claimed invention concerns kits comprising an unconjugated antibody, or antigen binding fragment thereof, that binds to an aminophospholipid in combination with a detectably-labeled anti-aminophospholipid antibody and/or an anti-cancer agent.

The Action at pages 13 and 14 includes a section titled "Conclusion", in which it is stated that the claimed invention as a whole is legally obvious and yet certain aspects of the claimed invention are not enabled by the specification. In the following sections, Applicants address each of these issues and show the Office's concerns to be unfounded and the claimed invention to be patentable.

Applicants also invite attention to co-pending application Serial No. 09/351,543 ("the '543 application"; Attorney Docket No. 4001.002200), in which claims directed to the treatment of vascularized tumors using an unconjugated antibody, or antigen binding fragment thereof, that binds to an aminophospholipid, optionally including imaging and combination therapy with other anti-cancer agents, have been allowed (allowed claims attached as **Exhibit B**; see claim 26 concerning combined treatment and imaging, and claims 28-40 concerning combination therapy with second anti-cancer agents). As the '543 application is based upon the same specification as the present application and has the same priority date, and as the allowed claims are directed to

therapeutic intervention using the same unconjugated anti-aminophospholipid antibodies or fragments thereof, allowance of the '543 application is highly pertinent to the present case.

VII. Rejection of All Examined Claims Under 35 U.S.C. § 112, Second Paragraph

The Action first rejects claims 1, 3-12, 14, 15 and 19-29 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and for failing to particularly point out and distinctly claim the subject matter of the invention. Although Applicants respectfully traverse, the Action's concerns are fully addressed.

A. Biologically Effective

The Action questions the clarity of the term "biologically effective amounts" in claim 1, stating "it is not clear to what type of effect is the claimed amount directed? For what purpose is this amount effective?" (Action at page 4).

Applicants first respectfully point out that claims are not interpreted in a vacuum, but are part of and are read in light of the specification. *Slimfold Mfg. Co. vs. Kinkead Industries, Inc.*, 1 USPQ2d 1563 (Fed. Cir. 1987). "A claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). In light of the incredibly detailed specification that supports the claimed invention, the term "biologically effective amounts" is sufficiently definite and no further explanation is needed in the claims.

Moreover, the statute requires that the description be concise as well as full. *In re Surrey*, 151 USPQ 724 (CCPA 1966). The claims as they presently stand are both succinct and definite, and thus meet the clear but concise requirements of 35 U.S.C. § 112, second paragraph. The claims should not be required to be so detailed as to obscure, rather than to particularly point out

and distinctly claim the invention. *In re Smythe and Shamos*, 178 USPQ 279, 286 (C.C.P.A. 1973).

The language "effective amount" also has express support in the case law. For example, the Board reversed a rejection of claims that recited "an effective amount" after determining that the phrase was definite in light of the disclosure. *Ex Parte Skuballa*, 12 USPQ2d 1570 (B.P.A.I. 1989). The present claims are also sufficiently definite when read in light of the disclosure.

Applicants further draw attention to *Application of Caldwell*, 319 Fed. 2d 254, 258 (C.C.P.A. 1963), holding that "'Effective amount' admirably states what is to be derived from the disclosure of the specification as to amount and we can see nothing 'critical' about the amount in determining the existence of patentable invention". Therefore, the case law indicates that the present claims are sufficiently definite in their recitation of "effective amounts" and the rejection is overcome.

Nonetheless, and without acquiescing with the present rejection in any way, Applicants point out that claims 39-42 are free from this rejection as the recited "effective amounts" are even more clearly related to specific biological functions[1].

B. Antigen-Binding Fragment

Next, the Action questions the recitation of "fragment thereof" in claims 1, 6, 7, 10, 11, 20, 21, 23 and 25-28, stating "it is not clear to what antigen-binding moieties is applicant referring?" (Action at page 4).

Applicants find it curious that the same term is found to be definite in examined claims 3, 8, 12, 15, 19 and 24. Applicants intend the term in rejected claims 1, 6, 7, 10, 11, 20, 21, 23 and

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[1] It will be understood that the term "biologically effective amounts" also includes the concept of provision "for a period of time(s) effective", so that the effective amounts may be administered in "one or more doses" (specification at pages 6, 15, 32-33, 110-113 and 119-121).

25-28 to mean the same as in acceptable claims 3, 8, 12, 15, 19 and 24, *i.e.*, the fragments or moieties that bind to the same antigen as the recited targeting antibody or detectably-labeled antibody.

It should also be noted that both "antibody" and "antigen-binding fragment thereof" are always used in reference to a defined target antigen. For example, "a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid"; "a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid"; and "a targeting antibody, or antigen-binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor stroma or tumor vasculature".

One of ordinary skill in the art would thus clearly understand the nature of the recited antigen-binding moieties from the language of the claims themselves. However, the claims are not interpreted in a vacuum, but are part of and are read in light of the specification. *Slimfold Mfg. Co. vs. Kinkead Industries, Inc., supra.* In light of the details in the present specification concerning antigen-binding fragments, portions and regions of antibodies, *e.g.*, at pages 17-18 and 98-99, a skilled artisan would be left in doubt regarding the clarity of the claims.

Applicants also respectfully point out that the term "antigen-binding fragment" occurs routinely in the claims of issued U.S. patents and is therefore *prima facie* definite. For example, in a recent computer-based search, Applicants found the term "antigen-binding fragment" to be present in the claims of 217 different U.S. patents (**Exhibit C**), which does not even include synonyms such as antigen-binding portions and regions. Attached as **Exhibits D, E, F and G** are just a few examples of U.S. patents in which the issued claims include terms such as antigen-binding fragment, portion and region.

The rejection is therefore overcome. Without agreeing with this rejection, Applicants also point out the term "antigen-binding fragment thereof" has been removed from the definition of the first antibody in each of claims 39-42.

C. Second Anti-Cancer Agent

The Action further questions the recitation "second anti-cancer agent" in claim 1, alleging this terminology to be vague as the claims apparently do not recite "a first" anti-cancer agent (Action at page 4).

In contrast, those of ordinary skill in the art would, in light of the present disclosure, clearly understand the "first" anti-cancer agent to be "the first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid", recited as the primary component of the claimed kits. After all, the claims must be interpreted in light of the specification, and the specification contains incredibly detailed teaching concerning the use of naked antibodies against aminophospholipids for use in cancer treatment. This understanding is clearly evident to the Office, as the Action itself characterizes the invention as pertaining to "the use of instant antibodies and fragment's [*sic*] thereof for cancer treatment" (Action at page 5).

In any event, the present specification discusses this very point, explaining:

> "In still further embodiments, the animals or patients to be treated by the present invention are further subjected to surgery or radiotherapy, or are provided with a therapeutically effective amount of at least a first anti-cancer agent. The 'at least a first anti-cancer agent' in this context means 'at least a first anti-cancer agent in addition to the naked anti-aminophospholipid antibody' (preferably anti-phosphatidylserine or anti-phosphatidylethanolamine). The 'at least a first anti-cancer agent' may thus be considered to be 'at least a second anti-cancer agent', where the naked anti-aminophospholipid antibody is a first anti-cancer agent. However, this is purely a matter of semantics, and the practical meaning will be clear to those of ordinary skill in the art."
>
> Specification at page 32, lines 1-9; emphasis added.

This rejection is therefore overcome. Without acquiescing with this rejection in any way, Applicants again point out that claims 39-42 are free from this rejection as they do not include the complained of "second anti-cancer agent" terminology.

D. Operatively Attached

Finally under this section, the Action questions the phrase "operatively attached" in claims 9 and 27, taking the position that it is not clear what is meant by this phrase or what type of chemical linkages are encompassed by the claimed invention (Action at page 4).

Applicants again respectfully point out that this rejection appears to have been formulated without reference to the specification, the understanding in the art, the controlling case law and other issued patents in the field.

Moreover, Applicants are perplexed that the "operatively attached and linked" terminology is acceptable in each of examined claims 23, 24, 25, 26, 27 and 28, and yet unacceptable in claims 9 and 27, wherein the intended meaning is the same.

The language of all such claims is clear on its face, meaning that the recited element comprises at least two regions, agents or component parts that are "operatively" attached or linked so that each maintains its function within the linked molecule. The operable association may be a direct linkage, including those formed from a variety of chemical conjugation techniques or by recombinant expression, or may be via an indirect attachment, including bispecific antibodies (specification at pages 19, 33-36, 58-59 and 137-146; Examples III; VI and VII).

Although not necessary in light of the detailed understanding in the art, the present specification also incorporates by reference a number of issued U.S. patents that detail the operative attachment of components within antibodies and immunoconjugates, including the

preparation of "immunotoxins" comprising cytotoxic agents and "coaguligands" comprising agents that directly or indirectly stimulate coagulation (specification at pages 137-146).

For example, for the purposes of even further supplementing the present teaching, the specification incorporates U.S. Patent No. 6,051,230 (**Exhibit E**), concerning compounds comprising intratumoral vascular targeting agents "operatively attached to therapeutic agents", and U.S. Patent No. 6,093,399 (**Exhibit F**), concerning compounds comprising tumor binding regions "operatively linked to coagulation factors" or antibodies thereto (specification at pages 139 and 143, respectively). Note that **Exhibit F**, in particular, addresses the Action's concerns regarding the various forms of operative linkage, including second antibody binding regions (claim 61); covalent bonds and chemical cross-linkers (claim 84); fusion proteins (claim 86); and avidin:biotin combinations (claim 87).

The claims of U.S. Patent Nos. 6,051,230 and 6,093,399 (**Exhibit E and Exhibit F**, respectively) are presumed valid and the standards of patentability applied in the examination of claims must be the same throughout the office. 35 U.S.C. § 282; MPEP 706 (see page 700-8, column 1). Accordingly, inclusion of the present claim language within the claims of the foregoing issued patents is *prima facie* evidence that the terms used are sufficiently definite under 35 U.S.C. § 112, second paragraph, and that the rejection is overcome.

All rejections under 35 U.S.C. § 112, second paragraph are therefore overcome and should be withdrawn.

VIII. Rejection of All Examined Claims Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1, 3-12, 14, 15 and 19-29 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not provide sufficient enabling support for kits

comprising an antigen-binding fragment of an antibody that binds to an aminophospholipid. Although Applicants respectfully traverse, the Action's concerns are fully addressed.

The present rejection seems to have been framed without reference to the detailed specification, the level of technical skill in the art, as evidenced by many issued patents in the field, and the controlling case law on 35 U.S.C. § 112, first paragraph. In fact, the rejection is *prima facie* improper, as the Action does not present sufficient reason to doubt the objective teaching in the specification. The law clearly provides:

> "As a matter of patent office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.
>
> *In re Marzocchi & Horton*, 169 USPQ 367, 370 (CCPA 1971; emphasis in original).

The Action alleges that there is no teaching identifying the various types of antibody fragments that may be used "for practicing the instant kits" (Action at page 4). Applicants first respectfully point out that a patent need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). The technical ability to make and use antigen-binding fragments of antibodies has existed in the art for over a decade. As such, Applicants have no burden to include such teachings in the specification.

Nonetheless, the Action is in error in the position that the specification does not include such a teaching, and appears to have overlooked the detailed guidance in the specification, *e.g.*, at pages 17-18, 69-74 and 98-99. The specification teaches that such antigen binding regions

and fragments include Fab', Fab, $F(ab')_2$, single domain antibodies (DABs), Fv, scFv (single chain Fv) fragments and the like. Although the techniques for making and using such antibody-based constructs and fragments are well known in the art, the specification provides incredibly detailed protocols for their preparation, *e.g.*, making Fab fragments and $F(ab')_2$ fragments by proteolysis (specification at pages 98 and 99).

The specification also provides significant details for preparing antigen-binding fragments of antibodies using contemporary technology and specifically incorporates by reference a number of issued U.S. patents that enable such techniques. For example, the use of phagemid libraries is described in great detail (specification at pages 69-74, U.S. Patent Nos. 5,658,727, 5,580,717; 5,427,908; 5,403,484; 5,223,409; 5,698,426, 5,667,988, 5,759,817 and 5,702,892). As explained in the specification and known in the art, the foregoing techniques result in the preparation of antigen binding regions of antibodies, such as complementarity determining regions, variable domains and single chain antibodies. The present rejection cannot be maintained in the face of so many issued U.S. patents, which provide *prima facie* evidence that the technical skill to prepare the claimed antibody fragments exists in the art.

The Action at the top of page 5 variously alleges "the claims encompass polypeptide [*sic*] which have amino acid substitutions other than the positions taught in the specification...Such teaching constitutes numerous possible amino acid sequences which are not supported by the instant disclosure. There is no guidance in the specification as to what alterations result in a functional fragments [*sic*]". These comments appear to constitute a formalistic rejection made without reference to the present claims or specification, or to the underlying technology.

Whilst there is a high degree of technical skill in the art, and the ability to make a broad range of recombinant antibody fragments is evident, *e.g.*, using phagemid libraries and affinity

maturation technology (note the large number of issued patents in this area), the claims do not rely on a teaching of amino acid substitutions at certain positions, as alleged in the Action. Many antigen-binding fragments of antibodies are simply made by limited proteolysis of the intact molecule, as described above (specification at pages 98 and 99).

This theme is continued at page 6 of the Action, the irrelevance of which is striking[2]. The claim language specifically recites "an antigen-binding fragment" of an antibody, which by its very nature, has an understandable and predictable tertiary structure, *i.e.*, one that binds to the same antigen as the reference antibody. The claimed fragments are not necessarily directed to "unknown chains of polypeptide", but in many regards are directed to the same polypeptide, simply cleaved from the intact antibody. Even where amino acid sequences are changed or otherwise selected, the ability to confirm that an antigen-binding fragment of antibody binds to the same antigen as an intact antibody has existed in the art for over a decade and is one of the most routine technical skills in biotechnology.

The Action further cites Fishman *et al.*, 1997 (*Int. J. Oncol.*, 10:901-904) in an attempt to support the position that the use of antigen-binding fragments of antibodies is unpredictable (Action at page 5). No reasoning is offered as to why Fishman renders the use of antigen-binding fragments unpredictable, but not the use of the antibodies themselves.

Should the Office maintain that Fishman renders the use of antigen-binding fragments unpredictable, Applicants most respectfully request that the particular portion relied upon be identified. Applicants also respectfully request that, should this line of reasoning be continued, the Office indicate what sections of Fishman are deemed appropriate to counteract the data in the

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[2] The reference by Ngo *et al.*, 1994, was not included with the Action. Although this renders the Action improper, Applicants elected not to contest the Action on this basis.

specification showing that practice of the presently claimed invention results in tumor reduction without side-effects (Example XII, specification at page 171, lines 13-14).

The continuing allegations that the specification fails to teach dosing information, side effect profile, safety, specific utility and effective amounts of antigen-binding fragments of anti-aminophospholipid antibodies (Action at page 5) continues the errors of the rejection. The specification teaches, and demonstrates to the satisfaction of the Office, that intact anti-aminophospholipid antibodies can be used to treat cancer *in vivo* with no observable toxicity (Example XII). The Office cites no evidence to doubt that antigen-binding fragments of such antibodies could be successfully used by those of ordinary skill in the art without undue experimentation in light of the present disclosure. Note that doses suitable for treating humans are described in the specification, *e.g.*, at pages 105-113.

In contrast to the position of the Action, the specification provides detailed guidance concerning the choice between antibodies and antigen-binding fragments thereof. For example, teaching that antibodies for use in inducing complement-mediated lysis will generally include the Fc portion of the antibody, but that complement-activated ADCC (antibody-dependent, cell-mediated cytotoxicity) does not require an Fc portion to achieve target cell lysis (specification from page 13, line 8 to page 14, line 13). It is also explained:

> "The choice of antibody construct may be influenced by various factors. For example, prolonged half-life can result from the active readsorption of intact antibodies within the kidney, a property of the Fc piece of immunoglobulin. IgG based antibodies, therefore, are expected to exhibit slower blood clearance than their Fab' counterparts. However, Fab' fragment-based compositions will generally exhibit better tissue penetrating capability.
>
> Specification at page 98, lines 10-14.

Without acquiescing with this rejection in any way, Applicants point out that claims 39-42 are free from this rejection as they do not include the use of antigen-binding fragments of the recited first antibody.

The rejection under 35 U.S.C. § 112, first paragraph is therefore overcome and the rejection should be withdrawn.

IX. First Rejection of All Examined Claims Under 35 U.S.C. § 103(a)

The Action next rejects claims 1, 3-12, 14, 15 and 19-29 under 35 U.S.C. § 103(a) as allegedly being legally obvious over Fishman *et al.*, *Intl. J. Oncol.*, 10:901-904, 1997 ("Fishman") and Umeda *et al.*, *J. Immunol.*, 143:2273-2279, 1989 ("Umeda") in view of Huang *et al.*, *Science*, 275:547-550, 1997 ("Huang"), U.S. Patent No. 6,197,278 to Blankenberg *et al.* ("Blankenberg") and WO 98/29453 ("the '453 application"). Although Applicants respectfully traverse, the Action's concerns are fully addressed.

A. The '453 application is not Available as Prior Art

Before a reference can be used as part of a rejection under 35 U.S.C. § 103(a), it must qualify as prior art under some provision of 35 U.S.C. § 102. The present application has an effective priority date of July 13, 1998. The cited '453 application is available as prior art only as of its publication date, which is July 09, 1998, *i.e.*, less than a year before the priority date of the present application. As such, the '453 application is only potentially available under 35 U.S.C. § 102(a) and can be removed as prior art using the mechanism embodied in 37 C.F.R. § 1.131.

Without agreeing with any aspect of the proposed rejection under 35 U.S.C. § 103(a) **(Section IX(b))**, Applicants hereby elect to remove the '453 application as prior art by submitting an inventors' declaration under 37 C.F.R. § 1.131. The enclosed declaration shows

that the present invention was made in the United States prior to July 09, 1998. Although not necessary to antedate the '453 application, from a time prior to July 09, 1998 through July 13, 1998, when the parent of the present application was filed, the inventors worked diligently to reduce to practice additional embodiments of the overall invention.

The exhibits attached to the declaration present evidence of the facts set forth and meet the requirements of MPEP 715. However, Applicants have elected to proceed under MPEP 715.07 and to remove the particular dates from the exhibits (see section entitled "ESTABLISHMENT OF DATES").

Paragraphs 12 through 14 of the declaration, and Exhibit A, provide evidence of the concept of the invention in the United States prior to July 09, 1998. The concept of using antibodies to aminophospholipids to thrombose tumor blood vessels and cause tumor regression in numerous types of solid tumors is documented in the Invention Disclosure form of Exhibit A. It is explained that the antibodies need not be linked to an effector molecule for activity, *i.e.*, that the antibodies function as unconjugated or "naked" antibodies.

At paragraphs 15 and 16, and in Exhibit B, the enclosed declaration provides evidence of successful *in vivo* cancer treatment using an unconjugated antibody to an aminophospholipid within the scope of the claims prior to July 09, 1998. Exhibit B shows the use of a species of anti-aminophospholipid antibody within the claimed invention to successfully treat tumors in controlled studies in animals in the United States prior to July 09, 1998.

Additional evidence of the progress of the invention prior to July 09, 1998 is described in paragraphs 17 through 19 of the declaration and in Exhibits C and D. Exhibit C of the declaration confirms that the role of Dr. Rote, who supplied certain biological materials for use

in the claimed invention, was confined to the provision of such materials to the inventors and does not in any way rise to the level of joint inventorship.

It is well established under the law that in order to antedate a reference using a declaration under 37 C.F.R. § 1.131, the declaration is only required to show "as much of the claimed invention as the reference happens to show". *In re Stempel*, 113 USPQ 77 (C.C.P.A. 1957). A reference applied against generic claims may be antedated as to such claims by an affidavit or declaration under 37 C.F.R. § 1.131 showing only a single species of the invention within the claimed genus. *In re Stryker*, 168 USPQ 372 (C.C.P.A. 1971); *In re Spiller*, 162 USPQ 614 (C.C.P.A. 1974). In the present case, Applicants have clearly shown an adequate basis to support possession of the claimed invention prior to the reference date. *In re Wakefield*, 164 USPQ 363 (C.C.P.A. 1970); *In re DeFano*, 157 USPQ 192 (C.C.P.A. 1968); *In re Clark*, 148 USPQ 665 (C.C.P.A. 1966); *In re Schaub*, 190 USPQ 324 (C.C.P.A. 1976).

The enclosed declaration under 37 C.F.R. § 1.131 thus establishes a date of invention in the United States prior to the July 09, 1998 publication date of the cited '453 application, and thus removes the '453 application as prior art.

As the '453 application is not available as prior art, the § 103(a) rejection based upon the combination of the '453 application with Fishman, Umeda Huang and Blankenberg is overcome and should be withdrawn.

B. The Proposed Combination Does Not Render the Invention Obvious

Even if the '453 application was available as prior art, the present combination of references fails to constitute a valid rejection under 35 U.S.C. § 103(a). The references have been improperly combined, and even if properly combined, the combination of references fails to suggest the claimed invention to one of ordinary skill in the art, and even if providing some

motivation towards the invention, the combination of references fails to provide the required reasonable expectation of success in achieving the invention.

For an obviousness rejection to be proper under 35 U.S.C. § 103(a), it is required that the cited prior art suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and that the prior art also convey to those of ordinary skill a reasonable expectation of success. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Dow Chemical Co., supra; In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

When, as in the present case, an obviousness rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. *In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). Even if every element of an invention can be found in the prior art, obviousness is not established in the absence of sufficient "motivation to combine". *Rouffet* at 1457-1458. A high level of skill in the art cannot be held to substitute for the required motivation to combine. *Rouffet* at 1458.

The Action acknowledges that neither Fishman nor Umeda "teach the combination of a anti- amino phospholipid [*sic*] antibody with a second anti-cancer agent for therapeutic kits", as in the claimed invention (Action at page 8, last paragraph). In fact, Umeda is apparently cited to show that monoclonal antibodies against phosphatidylserine could be prepared (Action bridging pages 7 and 8). Any attempt to show that an invention is within the level of ordinary skill in the art is misplaced in an obviousness rejection. In overturning two § 103(a) rejections as improperly relying on the high level of skill in the art, the Federal Circuit held:

> "The Board merely invoked the high level of skill in the field of the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness".
>
> *In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998).

Irrespective of the level of technical skill in the art, the three additionally cited references have been improperly combined with Fishman and Umeda, and are anyway irrelevant to the claimed invention, such that even if combined, the combination of references fails to suggest the claimed invention and particularly fails to provide a reasonable expectation of success in achieving the invention.

Huang is cited as disclosing methods of occluding tumor vasculature in solid tumors by targeting the cell surface domain of tumor vascular endothelial cells using a bispecific antibody-tissue factor conjugate (Action at page 8). The Action acknowledges that Huang does not teach targeting of aminophospholipids, but this is an understatement of the irrelevance of Huang to the claimed invention.

The present invention requires both an antibody against an aminophospholipid, and that the antibody be used in unconjugated form, *i.e.*, not linked to an effector such as a toxin or coagulant. As Huang is entirely limited to the use of targeting antibodies linked to effectors, such as tissue factor, Huang is at best irrelevant to the unconjugated antibodies of this invention. By focusing on conjugates, and making no reference to unconjugated antibodies for any therapeutic use, whether or not connected with tumor therapy, anti-vascular tumor therapy or combinations thereof, Huang actually teaches away from the simplicity of the present invention.

Applicants also note that the assessment of Huang in the Action bridging pages 8 and 9 appears confused in that MHC Class II is not a tumor cell surface marker.

As to aminophospholipids, not only does Huang not "teach" targeting of aminophospholipids (Action at page 8), Huang contains no discussion of aminophospholipid biology whatsoever, let alone any suggestion that aminophospholipids could be a target for anti-vascular tumor therapy using unconjugated anti-aminophospholipid antibodies. Accordingly, Huang has no relevance the invention and has been improperly combined with Fishman and Umeda.

Blankenberg is first cited as teaching "Annexin as a peptide with high affinity to anionic phospholipid surface of the cell membrane" (Action at page 8). As the claimed invention does not include annexin, Blankenberg is irrelevant to the issue at hand.

The Action next cites Blankenberg as teaching "targeting radio labeled Annexin V directed to a selected organ for any desired condition such as cancer", citing Blankenberg at column 12, lines 33-61 (Action at page 5). This is still irrelevant to the present invention, as any "targeting" in Blankenberg is limited to non-antibody conjugates and to diagnostics. Even as pertaining to radiolabeled annexin V, Blankenberg's connection to cancer is limited to "the detection of insufficient apoptosis when it should occur, e.g., tumors or cells infected with virus" (Blankenberg at column 12, lines 36-37).

The flaws in the Action's reasoning concerning Blankenberg extend from the irrelevance of annexin and non-antibody conjugates to the issue of therapy itself. The Action states that "Blankenberg suggests methods and compositions that can be used for both therapeutic and imaging purposes" (Action at page 8). However, no section of Blankenberg is cited in support of this assessment.

Applicants have studied Blankenberg and believe the document to be limited to diagnostic uses of annexins, and cannot identify any teaching or suggestion of therapy. Should the Office maintain that Blankenberg concerns methods and compositions that can be used for "therapeutic purposes", Applicants most respectfully request that the Office identify the particular section of Blankenberg that is believed to contain a teaching relevant to therapeutic purposes, and particularly, a teaching relevant to therapy using naked antibodies against aminophospholipids.

Blankenberg therefore has no relevance the invention and has been improperly combined with Fishman, Umeda and Huang.

The Action cites the '453 application[3] as concerning peptide drugs with specific affinity towards phosphatidylserine (Action at page 5). At the time of the second Action, only the English abstract for this Japanese document was available. Applicants have since obtained the English version of this document from the European Patent Office, which has been formally made of record in this case in a Supplemental Information Disclosure Statement.

Applicants have endeavored to study the translation of the '453 application, and find the document to be somewhat confusing. Nonetheless, it is clear from the enclosed translation that the '453 application does not concern anti-aminophospholipid antibodies *per se* or anti-aminophospholipid antibodies for use in any therapeutic embodiment, let alone any teaching or suggestion that an unconjugated anti-aminophospholipid antibody could be used in any aspect of tumor therapy.

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[3] Applicants respectfully point out that the cited '453 document is only a patent application and not a patent, as quoted in the Action at page 5.

Despite the Action's characterization of the "WO patent"[3] as concerning "methods and compositions that can be used for both therapeutic and imaging purposes", as the '453 application does not teach or suggest naked anti-aminophospholipid antibodies for use in any type of therapy, the '453 application is irrelevant to the claimed invention. This document has also been improperly combined with Fishman, Umeda, Huang and Blankenberg.

Overall, the Office has not met the legal burdens required to support a proper § 103(a) rejection. Accordingly, even if each of the five cited documents was available as prior art against the present invention, the § 103(a) rejection fails for at least the foregoing reasons of inadequate teaching or suggestion, improper combination and lack of reasonable expectation of success.

The first § 103(a) rejection is thus overcome and should be withdrawn.

X. Second Rejection of All Examined Claims Under 35 U.S.C. § 103(a)

Finally, the Action rejects claims 1, 3-12, 14, 15 and 19-29 under 35 U.S.C. § 103(a) as allegedly being legally obvious over the foregoing Fishman, Umeda Huang and Blankenberg documents in further view of U.S. Patent No. 5,632,991 to Gimbrone ("Gimbrone"), Dvorak *et al.*, *Cancer Cells*, 3(3):77-85, 1991 ("Dvorak") and the foregoing '453 application. Although Applicants respectfully traverse, the Action's concerns are fully addressed.

The '453 application is an integral part of this rejection. As established above, the '453 application is not available as prior art against the claimed invention as the inventors have removed this document by establishing a prior date of invention in the United States under 37 C.F.R. § 1.131.

As the '453 application is not available as prior art, the § 103(a) rejection based upon the combination of the '453 application with Fishman, Umeda Huang, Blankenberg, Gimbrone and

Dvorak is improper. Even if the '453 application was available as prior art, the present rejection fails as the additionally cited references have been improperly combined with the primary references, and even if combined, fail to cure the deficiencies of the first five cited references.

Various deficiencies of the earlier cited references are set forth above. As part of the present rejection, the Action includes a reference to "the antiaminophospholipid antibodies of Blackenberger's [*sic*, Blankenberg's] peptide drugs" (Action at page 11). Applicants respectfully point out that the terms "antibodies" and "peptide drugs" cannot be used in such a synonymous manner, even generally. When applied to Blankenberg, it is clear that such peptides are limited to radiolabeled annexins, which are not equivalent to naked antibodies against aminophospholipids.

Gimbrone is cited as disclosing "a targeting agent conjugated to an antibody directed to ELAM-1" (Action at page 9). Applicants are puzzled at this assessment of "a targeting agent conjugated to an antibody" and ask that the Office clarify this point if it is to be maintained.

The Action continues to assess Gimbrone as disclosing "the use of his targeting agent-therapeutic agent conjugate, alone or in combination with the antibody or antibody fragment" (Action at page 9). As the present invention is not directed to a targeting agent-therapeutic agent conjugate, either alone or in combination with anything, even if this assessment was accurate, Gimbrone would still have no relevance to the invention, which concerns naked antibodies against aminophospholipids. Although not critical to the many flaws in the rejection, Applicants believe that the Action may have misinterpreted these aspects of Gimbrone, which states that an anti-ELAM-1 antibody can be administered "either alone, or conjugated to a therapeutic agent" (Gimbrone at abstract).

Gimbrone is next characterized as disclosing "methods for detecting E-selectin expression within the body of a patient" and that inflammatory cytokines induce the expression of ELAM-1 (Action at pages 9 and 10). Even if these assessments were accurate, as the present invention concerns naked antibodies against aminophospholipids, and Gimbrone concerns ELAM-1, Gimbrone does not contain any teaching or suggestion relevant to the invention.

Dvorak is cited as concerning "various strategies that would have possibly improved the delivery of monoclonal antibodies to tumor vasculature; one of which is to identify the antigen that is uniquely expressed on tumor blood vessel endothelium" (Action at page 10). The present invention requires a naked antibody to an aminophospholipid. The Action acknowledges Dvorak as admitting "that there had been no antigens identified that would have been specific for tumor vessel endothelial surface" (Action at page 11). Yet somehow, despite the fact that no tumor blood vessel antigens were known, and that Dvorak does not mention any aspect of aminophospholipid biology, the Action still contends that Dvorak provides a suggestion relevant to the claimed invention. Should the Office maintain this position, Applicants respectfully request that those sections of Dvorak believed to be relevant to naked antibodies against aminophospholipids be identified.

The Action next states that "Dovorak [*sic*] et al express that antibodies directed against such antigens may be linked to either metabolic poisons or to radioisotopic cytotoxic [*sic*] and would have been expected to necrotize solid tumors by compromising their blood supply" (Action at page 10). Although the important deficiency in the lack of identification of any "such antigens" remains evident, this at best represents a hope towards the development of antibody *conjugates*, and the present invention is directed to *naked antibodies*, not to conjugates. Thus, Dvorak teaches away from the surprising simplicity of the claimed invention.

The text of the Action at pages 11 and 12 fails to meet any of the legal standard required to support a proper § 103(a) rejection. Therefore, even if each of the seven cited documents was available as prior art against the claimed invention, the present rejection fails for at least the foregoing reasons of inadequate teaching or suggestion, improper combination and lack of reasonable expectation of success.

The second § 103(a) rejection is thus overcome and should be withdrawn.

XI. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and enclosed documents, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner Shareeh have any questions or comments, or identify any informalities, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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